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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,163	12/20/2001	Sanjay Lakhotia	AM100039	1674

25291 7590 12/14/2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,163	LAKHOTIA ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *25 April 2--3*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Specification Objection

1. The use of the trademark has been noted in this application. For example, page 8, line 33 and throughout the specification. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Correction is required.

Claim Objections

2. Claim 2 recites "Mg+2" and "Ca+2" which should be changed to "magnesium" and "calcium" respectively, at the first occurrence in the claims. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-16 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain trademarks, for example Tris™ or Triton™. The trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 4-5 and 7-12 are rejected under 35 U.S.C. 102(e) as anticipated Green et al *(U.S. Patent No. 5,780, 601, published July 14, 1998).*

Claims 4-5 and 7-12 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Green et al teach a method of purifying bacteria using detergents such as Triton™ (column 4). Green et al teach that in a preferred embodiment the outer membrane components are prepared by differential solubilization of the inner membranes using Triton™ in HEPES-NaOH and $MgCl_2$. Green et al teach that a subfraction of the preparation of the outer membrane components which is rich in

protein "e" (outer membrane protein P4 from *Haemphilus influenzae)* can be produced by extraction with an aqueous solution (column 4). Green et al teach that the protein "e" from the outer membrane cell wall complex can be then achieved by a two-step differential solubilization with sulfobetaine detergents (column 4). Green et al teach that the first step comprises an aqueous solution of Zwittergent™ to remove other outer membrane proteins other than protein "e" (column 4). Green et al teach that the residual insoluble components are then extracted with an aqueous solution of Zwittergent™ and this fraction results in the solubilization of protein "e"(column 4). Green et al teach that this process is performed in a homogenizer (column 14) since the instant specification teaches that a homogenizer is a microfluidizer (page 10 of the specification). Green et al teach that recombinant protein "e" can be isolated and purified by differential solubility (column 9).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

5. Claims 4-5 and 7-12 are rejected under 35 U.S.C. 102(b) as anticipated Green et al *(Infection and Immunity, Sept. 1991, p. 3191-3198).*

Claims 4-5 and 7-12 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Green et al teach a method of purifying e protein after contaminating proteins were removed by extraction with Tris HCL, EDTA in sarcosyl (buffer A) followed by extraction with Zwittergent™ in buffer A (page 3191). Green et al teach that in e protein was solubilized by extraction of the insoluble fraction with Zwittergent™ in buffer A (page 3192). Green et al teach that e protein was partially purified by passage over a DEAE Biogel-A column equilibrated with buffer A containing Zwittergent™ (page 3192). The soluble e protein was then absorbed onto a hydroxylapatite column equilibrated with buffer and eluted with sodium phosphate (page 3192). Green et al teach that the eluted e protein was precipitated with ethyl alcohol washed with octylglucoside, Tris, HCL and solubilized in buffer A containing Zwittergent™ (page 3192). The claim limitation "wherein the process occurs in a microfluidizer" would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material

method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-7 and 13-16 are rejected under 35 U.S.C. 103(a) as unpatentable over Anilionis et al *(U.S. Patent No. 5098,997, published March 24, 1992)* in view of Kolbe *(U.S. Patent No. 5,276, 141, published January 4, 1994).*

Claims 1-7 and 13-16 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Anilionis al teach a method isolating and purifying of native and recombinant inner and outer membrane proteins from *Haemophilius influenzae* (columns 26-27). Anilionis et al teach that *Haemophilius influenzae* incubated in medium and centrifuged to form a cell pellet (columns 26-27). Anilionis et al teach that the cell pellet was suspended in HEPES-NaOH, EDTA and placed in a cell disruptor (columns 26-27).

Anilionis et al teach that the total membrane fraction was separated into inner and outer membrane components by extraction with sarcosyl in HEPES-NaOH (column 27).

Anilionis et al teach do not teach divalent cations such as calcium to stabilize the outer membrane proteins.

Kolbe teaches that divalent metal ions such as calcium can form complexes with proteinaceous compounds (column 1). Kolbe teaches that divalent metal ions are commonly used in processes of purifying proteins either as coupling agents for affinity chromatography or to precipitate proteins from liquid medium (column 1).

It would be *prima facie* obvious at the time the invention was made to add the divalent metal ions as taught by Kolbe to the process of purifying protein of Anilionis et al because divalent metal ions such as calcium can form complexes with proteinaceous compounds and divalent metal ions are commonly used in processes of purifying proteins either as coupling agents for affinity chromatograph or to precipitate proteins from liquid medium. It would be expected barring evidence to the contrary, that the use of diavalent ions in a process of purifying proteins would be effective in preparing stabilized proteins.

7. Claims 1-7 and 13-16 are rejected under 35 U.S.C. 103(a) as unpatentable over Yan-Ping et al *(Vaccine, Vol. 15, No.9, p. 976-987, 1997)* in view of Kolbe *(U.S. Patent No. 5,276, 141, published January 4, 1994).*

Claims 1-7 and 13-16 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Yan-Ping et al teach a method isolating and purifying recombinant and native P6 outer membrane proteins from *Haemophilius influenzae* (pages 977-978). Yan-Ping et al teach that *Haemophilius influenzae* centrifuged to form a cell pellet (gage 978). Yan-Ping et al teach that the cell pellet was extracted with NaCl (page 978). Yan-Ping teach that the pellet was resuspended in Tris-HCL containing Triton and EDTA (page 978) and centrifuged (page 978). Yan-Ping et al teach that the pellet was resuspended in Tris-HCL in sodium deoxycholate and P6 protein was precipitated using ethanol (page 978). Yan-Ping et al teach that the P6 fraction was purified using a column to remove protein contaminants (page 978). Yan- Ping et al teach P6 was eluted in Tris-HCL buffer and Triton (page 978).

Yan-Ping et al do not teach divalent cations such as calcium to stabilize the outer membrane proteins.

Kolbe teaches that divalent metal ions such as calcium can form complexes with proteinaceous compounds (column 1). Kolbe teaches that divalent metal ions are

commonly used in processes of purifying proteins either as coupling agents for affinity chromatography or to precipitate proteins from liquid medium (column 1).

It would be *prima facie* obvious at the time the invention was made to add the divalent metal ions as taught by Kolbe to the process of purifying protein of Yan-Ping et al because divalent metal ions such as calcium can form complexes with proteinaceous compounds and divalent metal ions are commonly used in processes of purifying proteins either as coupling agents for affinity chromatograph or to precipitate proteins from liquid medium. It would be expected barring evidence to the contrary, that the use of diavalent ions in a process of purifying proteins would be effective in preparing stabilized proteins.

Pertinent Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure (Deich et al, *(U.S. Patent No.5,110, 908, published May 5, 1992)* and Murphy et al, *(European Patent Application No. 0 389 925 A1, published October 3, 1990)*.

Status of Claims

9. No claims are allowed.

MARK NAVARRO
PRIMARY EXAMINER

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
December 2, 2004